Ahmed A. Moustafa*, Mohamed Salama, Roseanne Peak, Richard Tindle, Amir Salem, Szabolcs Keri, Błażej Misiak, Dorota Frydecka and Wael Mohamed

Interactions between cannabis and schizophrenia in humans and rodents

Abstract: In this review, we provide an overview of the relationship between cannabis use and the development of schizophrenia, using both animal and human studies. We further discuss the potential neural mechanism that may mediate the relationship between cannabis use and schizophrenia symptoms. We finally provide clinical implications and future studies that can further elucidate the relationship between cannabis and schizophrenia.

Keywords: cannabis; endocannabinoid receptors; negative symptoms; positive symptoms; schizophrenia.

Introduction

Schizophrenia is one of the most common neurodevelopmental disorders (Khandaker et al., 2011). It is manifested with various symptoms including positive (hallucinations, delusions, and though disorder), negative (loss of motivation, anhedonia, and lack of affect), and cognitive deficits (Kohen, 2004) as well as metabolic abnormalities (McEvoy et al., 2005). Adolescence is a period with specific psychosocial challenges and changes in the brain that may be associated with an increase in the probability of substance abuse (van Nimwegen et al., 2005). The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) states that the onset of schizophrenia typically occurs between the late teens and the mid-30s. It is apparent that some aspects of the disorder are observed during the early adolescent period before an individual presents with a full spectrum of schizophrenia symptoms (Maki et al., 2005). Schizophrenia is considered to be a neurodevelopmental disorder (Weiser et al., 2004) with its pathogenesis stretching back to gestation and early childhood (Cannon and Murray, 1998).

There is a growing interest in the link between schizophrenia and substance abuse. Substance abuse comorbidity is a common problem for patients with schizophrenia and related psychotic disorders (Fowler et al., 1998). Glassman (1993) suggested that apathy and lack of motivation, which is a characteristic of negative symptoms in schizophrenia, is what one would expect with diminishing activity of the brain's reward system. It is suggested that the increase in dopaminergic activity, which mediates positive reinforcement, is the basis of this self-medication hypothesis. Previous studies have estimated that up to 60% of people with schizophrenia have comorbid substance abuse (Fowler et al., 1998; Margolese et al., 2004). In another study, schizophrenia patients in comparison to the healthy population have been found to have a twofold increase in rates of cannabis use. Further, it has been found that cannabis is the most commonly used illicit drug among patients with schizophrenia, with a 64.4% lifetime use (Barnes et al., 2006). Koskinen et al. (2010) found that approximately 25% of patients with schizophrenia have been diagnosed with a comorbid cannabis use disorder (CUD).

Previous work has shown that among people with schizophrenia life expectancy is estimated to be 20% less than in the general population (Mortensen and Juel, 1993; McCreadie and Kelly, 2000). The use and abuse of alcohol, marijuana, psychostimulants, and other drugs

*Corresponding author: Ahmed A. Moustafa, School of Social Sciences and Psychology, Western Sydney University, Sydney 2214, New South Wales, Australia; and Marcs Institute for Brain and Behaviour, Western Sydney University, Sydney 2214, New South Wales, Australia, e-mail: a.moustafa@westernsydney.edu.au
Mohamed Salama: School of Medicine, Mansoura University, Mansoura 35516, Egypt
Roseanne Peak, Richard Tindle and Amir Salem: School of Social Sciences and Psychology, Western Sydney University, Sydney 2214, New South Wales, Australia
Szabolcs Keri: Nyírő Gyula Hospital, National Institute of Psychiatry and Addictions, 1124 Budapest, Hungary; Department of Physiology, Faculty of Medicine, University of Szeged, 2371 Szeged, Hungary; and Department of Cognitive Science, Budapest University of Technology and Economics, H-1111 Budapest, Hungary
Błażej Misiak: Department of Genetics, Wroclaw Medical University, 1 Marcinkowski Street, 50-368 Wroclaw, Poland
Dorota Frydecka: Department of Psychiatry, Wroclaw Medical University, 10 Pasteur Street, 50-367 Wroclaw, Poland
Wael Mohamed: International Islamic University Malaysia, Jalan Gombak, Selangor 53100, Malaysia; and Clinical Pharmacology Department, Menoufia Medical School, Menoufia University and American University in Cairo, Cairo 75419, Egypt

is commonly found to be comorbid with psychiatric conditions in adolescents (Deas and Brown, 2006). Specifically, cannabis use among patients with schizophrenia is approximately 10 times higher than in the global population (Koskinen et al., 2009) with a lifetime abuse ratio of five or six times higher than the general population (Regier et al., 1990). Furthermore, there is an inverse correlation between the amount of cannabis use in adolescence and the age of onset of psychosis (Large et al., 2011). Importantly, early onset psychosis also occurs alongside deficits in cognitive control (Solowij and Michie, 2007), more severe course of symptoms, and poorer treatment outcomes (Clausen et al., 2013).

Evidence suggests that the intravenous administration of tetrahydrocannabinol (THC) to healthy participants induces positive (Barkus et al., 2011) and negative psychosis-like symptoms (Morrison and Stone, 2011). A wide range of animal and human research suggests that the use of cannabis during adolescence prompts psychosis and cognitive impairment (Ehrenreich et al., 1999; Arseneault et al., 2002; Schneider and Koch, 2003). However, there is a lack of causal evidence to show that increased cannabis use over time also increases the incidence of schizophrenia (Moore et al., 2007). Nevertheless, cannabis use may exacerbate symptoms of schizophrenia and increase the risk of predisposed individuals developing schizophrenia (Degenhardt et al., 2003).

Prior review articles in schizophrenia and cannabis

Here, we discuss prior reviews on the relationships between cannabis and schizophrenia and novel approaches we are taking in our review. Radhakrishnan et al. (2014) conducted a literature review and have posited that acute exposure to cannabinoids can produce a full range of symptoms including psychophysiological irregularities and cognitive deficits. Further, these impairments and deficits would appear to be analogies to symptoms of schizophrenia. The review also found that cannabis can have negative consequences on pre-existing psychosis, triggering relapse and exacerbating symptoms (Radhakrishnan et al., 2014). Radhakrishnan et al. (2014) further suggested that the majority of users who consume cannabis do not experience any kind of psychosis, and the relationship between cannabinoids and psychosis fulfills many but not all of the traditional criteria for causality. Taking into consideration the above information, it is questionable that there is a single causative factor.

Further, Konings et al. (2012) suggest that childhood maltreatment regulates the interaction between psychosis and cannabis in an extra-linear, dose-dependent manner. Konings et al. (2012) further suggest that self-medication is also unlikely to account for the interaction between cannabis use and psychosis.

It has been reported that there is a four-fold increase in the rates of cannabis use over the last 40 years (Zammit et al., 2008), yet this has not resulted in an increase in prevalence of schizophrenia. Further, there is disagreement whether schizophrenia is on the decrease or increase (Hickman et al., 2007). The inconsistency between the recent changes in the rates of cannabis consumption and relative stability of schizophrenia prevalence may be a reflection of schizophrenia being a very heterogeneous illness, encompassing multiple sub-types. Rounsaville (2007) posits that cannabis-induced psychotic disorder is a specific subtype of the schizophrenia spectrum. Further, it may have to do with the specific psychoactive ingredients of the cannabis plant.

The main psychoactive ingredient of the cannabis plant is D-9-THC. In healthy individuals and non-schizophrenia patients, D-9-THC can impair the memory as well as induce anxiety and psychotic symptoms (D'Souza et al., 2005). Further, it has been found that D-9-THC can impair psychomotor control (Ramaekers et al., 2006). In contrast, schizophrenia patients exposed to D-9-THC may experience exacerbated existing memory impairments, anxiety, and psychotic symptoms (D'Souza et al., 2005). Furthermore, D-9-THC is thought to be the psychoactive ingredient most likely to be responsible for the increased risk of developing schizophrenia following regular cannabis use (Moore et al., 2007).

Interestingly, cannabis had another major psychoactive ingredient known as cannabidiol (CBD) which is has been found to have no negative impairments on memory or other cognitive functions (Fadda et al., 2004; Ilan et al., 2005). Further, it is believed that CBD possesses antipsychotic properties (Zuardi et al., 1982; Morgan and Curran, 2008).

Bhattacharyya et al. (2010) found, using fMRI scans on participants, that D-9-THC and CBD had opposite activation directions in the context of a series of tasks that engaged a diversity of brain regions and cognitive processes, specifically, attenuation of striatal activation by D-9-THC and the opposite effect of CBD suggesting inhibition and facilitation of the recall responses (Bhattacharyya et al., 2010). Further, the opposite effects of D-9-THC and CBD found on the amygdala activation during fear processing are consistent with the notion of exacerbating and reducing pre-existing anxiety symptoms (Bhattacharyya et al., 2010).

Bhattacharyya et al. (2010) reported that D-9-THC had concurrent effects on psychotic symptoms while CBD had no effect on psychotic symptoms. These findings appear to be consistent with that of Zuardi et al. (1982) who suggested that CBD may only have antipsychotic effects in patients with pre-existing psychotic symptoms. Further, a systematic literature review was conducted, finding concurrent results which suggested that CBD appears to have the ability to counteract psychotic symptoms and cognitive impairment and psychosis associated with cannabis use (Iseger and Bossong, 2015).

It should be noted that the results of this study have their limitations. Firstly, the administration of the active D-9-THC and CBD were administered orally or intravenously, and it is unclear if delivery system of the ingredients will have any effects on the results. Secondly, while isolating D-9-THC and CBD, it would seem prudent to measure the interplay of all psychoactive ingredients of the cannabis plant to account for any compounding effects that may confound the above results when cannabis is used recreationally. Thirdly, the sample size for this study was quite small, and the results should be interpreted with caution.

Degenhardt et al. (2003) posit that changes in the occurrence of cannabis use may potentially alter the age of onset, number of incidence, and prevalence of psychosis. However, Degenhardt et al. (2003) trend model suggested that it is unlikely that cannabis had caused psychosis that would not otherwise have occurred, however, the first episode psychosis cases who used cannabis were younger than non-users (Degenhardt et al., 2003). Further, the data suggested that it is likely that cannabis use would cause relapses to psychosis (Degenhardt et al., 2003), which is not consistent with other studies (Bhattacharyya et al., 2010). It should be noted that modeling of any trends holds its limitations as it is based on assumptions not otherwise empirically tested.

Further, it is well known that schizotypal personality disorder (SPD) traits have been found to be more prevalent in relatives of schizophrenia patients (Appels et al., 2004) and that they typically share similar genetic traits to schizophrenia patients (Fanous et al., 2007). Further, individuals with SPD commonly exhibit social deficits less prominent than but similar to schizophrenia (Dickey et al., 2005). Previous studies have examined cannabis use as a correlate of SPD and its associated dimensional traits thought to contribute to risk for psychosis in order to explore the affiliation between psychotic symptoms and cannabis use. Numerous studies have found associations between cannabis use and positive schizotypal features (Barkus and Lewis, 2008; Esterberg et al., 2009;

Najolia et al., 2012). However, it should be noted that these studies predominately studied university students using self-report measures which may have confounded the results of the above mentioned studies.

Furthermore, it has been found that there is a significant positive correlation between schizotypy scores and cannabis use (Skosnik et al., 2001) as well as an association between cannabis use and negative, disorganized, and positive schizotypal traits (Bailey and Swallow, 2004). It has been posited that these results indicate that the risk of SPD and associated psychosis increases with greater use of cannabis, and compared to non-users, greater cannabis use showed significantly increased risk of SPD symptoms (Davis et al., 2013). However, much like the research with schizophrenia patients and cannabis, there is some controversy as it has also been shown that cannabis is associated with lower negative schizotypal traits in users than in non-users (Schiffman et al., 2005).

Alongside SPD, schizoaffective disorder is also related to schizophrenia as both disorders have been placed under the 'Schizophrenia Spectrum and Other Psychotic Disorders' section of DSM-5. Schizoaffective disorder commonly presents with features of schizophrenia taking place concurrently with a mood episode (Malaspina et al., 2013). Further, there is a significant similarity in the genes contributing to SPD, schizoaffective disorder, and schizophrenia (Cardno and Owen, 2014). It has been found that there is a strong comorbidity between schizoaffective disorder and CUD (Koskinen et al., 2010), as similar to SPD and schizophrenia. Further, the literature would suggest that cannabis usage is correlated with significantly lower quality of life, impacting negatively on patients with schizoaffective disorder (Foti et al., 2010). However, it should also be noted that it has been found that cannabis use is correlated with improved quality of life presenting in relief from side effects of antipsychotic medications and psychiatric symptoms, depression, and boredom (Goswami et al., 2004). It is clear that there is much controversy in our current understanding of cannabis use and its effect on the schizophrenia spectrum and other psychotic disorders and that further research is required to resolve existing conflicting results.

Cannabis, schizophrenia, and cognition

While research reliably illustrates cognitive impairment of specific cognitive domains as a common symptom

expression of schizophrenia, findings on the effects of cannabis use are varied. In contrast to the healthy, non-diagnosed population, it is mainly agreed upon that cannabis users have yielded poorer neuropsychological functioning and have comparable cognitive performance between users and non-users (Pope et al., 2001). This being said, there have been research findings both consistent and inconsistent with the common cognitive impairment with schizophrenia patients. It has been found that approximately 80% of patients that used cannabis presented with more exacerbated and global deficits across cognitive domains. However, it has also been reported that schizophrenia patients with a history of cannabis use have less severe cognitive deficits (Stirling et al., 2005).

Regardless of agreement on cognitive deficit, the moderating character of cannabis use on cognitive domains such as special abilities, memory and learning, attention, and intelligence remains unclear. Interestingly, cannabis use has been correlated with higher rates of psychotic symptoms and aberrant brain functioning (D'Souza et al., 2005) and is thought to hinder prognosis (Linszen et al., 1994). These findings suggest that cannabis may have differential effects on a susceptible schizophrenia user as compared to a healthy non-diagnosed user.

Very little is known about the cognitive function of patients suffering from the combined effects of schizophrenia and cannabis use. To date, there have been inconsistent findings of the effects of cannabis on neurocognition. In the current literature, there are studies examining the effects of cannabis use on cognition in schizophrenia that have found superior neuropsychological functioning (Schnell et al., 2009), while other studies have observed poorer cognitive performance (Mata et al., 2008). Further, some studies were unable to find a significant difference in some cognitive tasks when comparing patterns of cannabis use among schizophrenia patients (Jockers-Scherübl et al., 2007; Sevy et al., 2007).

Yucel et al. (2012) conducted a meta-analysis with a focus on the effects of cannabis on cognition in schizophrenia patients. The inclusion criterion for this meta-analysis was whether the most preferred substance of the sample was cannabis. As a result, this analysis included studies where not all patients in the substance-using group were abusing cannabis, and as such, the findings of the cannabis-using subgroup were confounded by concurrent drug use.

Rabin et al. (2011) also conducted a meta-analysis researching the neurocognition in schizophrenia patients with no other current comorbid substance use. The results suggested a significant superior neurocognitive performance in cannabis-using schizophrenia patients compared to non-using schizophrenia patients. However, Rabin et al. were not able to determine effect size differences due to psychotic diagnosis, the combined effects of cannabis use and schizophrenia, nor the effects of cannabis use alone.

Cannabis, schizophrenia, and positive and negative symptoms

Further, there is disagreement on the effects of cannabis on both positive and negative symptoms in schizophrenia patients. There are findings not only to support elevated levels of positive symptoms in comparison to non-user schizophrenia patients without cannabis use (Degenhardt et al., 2007), although other studies found no difference in positive symptoms (Green et al., 2004). Similarly with negative symptoms, there is evidence to support no difference between schizophrenia patients who used and those who did not use cannabis (Stirling et al., 2005), as well as evidence to support decreased levels of negative symptoms (Koskinen et al., 2009) in schizophrenia user versus non-user patients. In 2008, Potvin et al. (2008) conducted a meta-analysis to determine to which extent better neuropsychological functioning might be found among patients with schizophrenia and substance use disorders. Potvin et al. (2008) concluded that these schizophrenia patients do not represent a homogeneous group and that future investigations should consider intermediate factors to define subgroups such as first time or lifelong user and drug of choice.

In summary, the association between cannabis and psychosis has been established for many years. However, it is still misunderstood whether cannabis use is a contributing cause for psychosis. The current review will briefly summarize the nature of the association between cannabis use and the development of psychosis and current thinking on the underlying neurobiology for their interaction. This will help provide a better understanding of the links between cannabis use and schizophrenia. An additional goal of the present paper is to propose possible prevention opportunities in the target population especially cannabis users.

The endocannabinoid system

Cannabis is one the most widely used illicit substances in the Western world (Smart and Ogborne, 2000; Von

Sydow et al., 2001) and one of the oldest used drugs with almost 60 different cannabinoids. Among many psychoactive chemicals in cannabis, the most active substance in cannabis is Δ9-trans-THC (Gaoni and Mechoulam, 1971). The endocannabinoid system (ECS) was discovered in the early 1990s and is composed of cannabinoid receptors (CB1 and CB2), ligands (anandamide), and protein for synthesis and degradation (Ameri, 1999; Pertwee, 2006; De Petrocellis and Di Marzo, 2010). ECS is widely distributed throughout the human body and affects immune response, learning, pain, body temperature, motor coordination, apoptosis, and others. Furthermore, the ECS malfunctions in schizophrenia patients, with impaired CB1 functions (Ameri, 1999), altered densities (Dean et al., 2001), gene polymorphism (Leroy et al., 2001), elevated anandamide ligand level in cerebrospinal fluid (Leweke et al., 1999; Giuffrida et al., 2004), and altered CB1. In light of this, there is a strong tie between cannabis and psychosis (D'Souza et al., 2005). For example, schizophrenia patients have more psychotic relapses and hospitalization with cannabis abuse (Linszen et al., 1994). Schizophrenia patients also experience a two- to three-fold increase in psychotic symptoms (Arseneault et al., 2002; Semple et al., 2005) including positive symptoms and negative symptoms (Solowij and Grenyer, 2002). Furthermore, cannabis affects cognitive functions, such as selective attention in patients with schizophrenia (Emrich et al., 1997; Pope et al., 2001).

The reasons for the interplay between schizophrenia symptoms and cannabis use remain unclear. One possible explanation is dopamine sensitization in schizophrenia (Moghaddam and Krystal, 2003); this makes patients more sensitive to the effects of cannabis (Chambers and Self, 2002; Tsiridis et al., 2003). Another explanation may be disturbance in the ECS (Potvin et al., 2008). A wealth of evidence supports the hypothesis that dysfunction of the cerebral ECS may be involved in the pathology of schizophrenia (for review, see Ujike and Morita, 2004; Barnes et al., 2006).

Cannabis-schizophrenia interplay in animal models

There is mounting evidence that the underlying pathophysiology in schizophrenia involves impairment in dopamine, glutamine, and acetylcholine (Moghaddam and Krystal, 2003). Surprisingly, these neurotransmitters stimulate N-arachidonoylethanolamine synthesis and release in rodents (Leweke et al., 1999; Stella and Piomelli, 2001). There are many available animal models which study schizophrenia, with pros and cons for each one. The weakness of most available models is that they are either not developmental or not consistent with the neuropathology of the disorder (Harrison and Eastwood, 2001; Tunbridge et al., 2004). There have only been a few studies that analyze addiction using rodent models of schizophrenia, which have varied from *in vitro* analyses (Rodvelt et al., 2008a,b), to sensorimotor gating (Radek et al., 2006), to alleviating cognitive impairments (Rezvani et al., 2008). Thus, there is a dearth of information regarding addiction's effects on the brain and behavior using a rodent model of schizophrenia.

Animal models of schizophrenia are of paramount importance to better understand the pathogenesis of this disorder. This is due to the difficulty in controlling the complex nature between genetics and environment in clinical studies (Calvigioni et al., 2014). An ideal animal model is able to recapitulate the pathology and progression of the disease (Langer and Halldin, 2002). Several pharmacological models exist that could introduce some feature of schizophrenia; these include models affecting serotonergic, glutamatergic, GABAergic, dopaminergic, and opioid systems (Steeds et al., 2015). However, in this review we will focus on animal models manipulating the cannabinoid system.

The first models of cannabinoid manipulation were induced through THC which is the primary active component of cannabis. THC administration to rodents led to an impairment of memory functions and impaired prepulse inhibition coupled to persistent behavioral changes. These effects were controlled by antipsychotic therapy administered to the animals (Schneider and Koch, 2003; Rubino et al., 2008; Realini et al., 2009).

More recently, animal models were induced to study the impact of cannabis use in adolescence (Hutchings and Dow-Edwards, 1991). Some of these models showed some schizophrenia-related behavioral abnormalities (Malone et al., 2010). This was attributed to cannabis affecting the maturational change that normally occurs in the endocannabinoid system during adolescence (Rubino and Parolaro, 2015). Furthermore, animal models support the interplay between genetic predisposition and environmental exposure to cannabis. Tantra et al. (2014) revealed that chronic exposure of juvenile St8sia2$^{-/-}$ mice to Δ9-THC affects learning and memory, which is contrary to wild type mice exposed to the same regimen.

The effect of prenatal exposure to cannabis has also been investigated to further understand the interplay between cannabis use and schizophrenia. An animal study showed that prenatal exposure to THC led to

ultrasonic vocalization of rat offspring, which is similar to human earlier fetal distress (Trezza et al., 2008). More interestingly, parental germline exposure to cannabis led to molecular changes in offspring striatum denoting that fetal development may be affected through prenatal exposure, either from germline transmission or direct exposure during pregnancy (Szutorisz et al., 2014). Nevertheless, animal models offer a unique opportunity to study the impact of cannabis on schizophrenia not only as a contributory or protective agent but also as provider of insight into the differential response to cannabis in patients with schizophrenia. Recently, Gallo et al., studied this problem using neonatal ventral hippocampus lesions in rats (Gallo et al., 2014). Both THC and WIN55, 212-2 (a cannabinoid receptor agonist) were used. In general, they showed that adult schizophrenic animals were differentially responsive to cannabis motivational effects. Most animal studies focused on the contributory role of cannabinoids in inducing schizophrenia or similar effects in studied animals. However, others proposed cannabis as a potential therapy for some schizophrenic manifestations. Spano et al. (2013) showed that cannabinoid self-administration attenuated the psychotomimetic effects of phencyclidine in rats. Based on these results, cannabis may exert protective effects on positive schizotypic manifestations in animal models. As can be seen, animal models will contribute largely to our understanding of schizophrenia pathogenesis and treatment and to identify the negative and positive aspects of cannabis use in schizophrenia.

Cannabis-schizophrenia interplay in humans

There are many hypotheses that explain the high prevalence of cannabis use among patients with schizophrenia. The self-medication hypothesis assumes that patients consume cannabis to alleviate their symptoms and reduce unpleasant secondary effects of their medications (Awad and Voruganti, 2015). There is no empirical support for this hypothesis, given that cannabis aggravates rather than improves psychotic symptoms. On the other hand, others show that the ECS is dysregulated in schizophrenia with different sensitivity to the psychoactive effects of cannabis (Muller-Vahl and Emrich, 2008; Potvin et al., 2008).

Studies found that in healthy populations, cannabis use can cause paranoia, hearing voices, and schizophrenia. Such reports of the link between cannabis use and schizophrenia were found in different countries including the US, UK, Australia, South Africa, India, Sweden, and Pakistan. Other studies also found that cannabis use can also lead to psychotic episodes in patients with schizophrenia (Negrete et al., 1986); these effects were found to be related to the dose of cannabis taken. The link between cannabis use and schizophrenia was also reported in a longitudinal study with Swedish conscripts (Zammit et al., 2002). One limitation of this study (as well as most other studies) was the reliance on self-reports and failure to collect urine samples to identify cannabis use and dosage. Another longitudinal study found that cannabis use at a younger age increased the risk of developing schizophrenia than drug use at an older age (Arseneault et al., 2002). Furthermore, there is attentional dysfunction in patients with schizophrenia who use cannabis simultaneously along with sensory cortical circuit affection.

The exact biological link between cannabis use and schizophrenia is not clear (Shrivastava et al., 2014). Some studies suggested that changes to dopamine and endocannabinoid receptors play a role. At the biological level, the active component in cannabis (i.e. THC) activates endocannabinoid receptors as well as increases presynaptic dopamine in different cortical areas. Further, it has been reported that schizophrenia is associated with changes to both dopamine and endocannabinoid receptor structure and function.

Although the incidence of schizophrenia among cannabis users is higher than in the general population, it is still unknown what factors or individual differences make some but not others develop psychosis and schizophrenia. One study, however, found that current daily use and consuming cannabis for more than 5 years was a strong predictor for having schizophrenia symptoms. It is also not known whether there are personality traits that may be risk factors for both cannabis use and schizophrenia, so it is not known if the link between cannabis use and schizophrenia is causal or not. Future studies should also test whether schizophrenia symptoms can persist after drug use abstinence. Further, given that most drug users often consume more than one kind of drug, it is not unlikely that other drugs of abuse (e.g. amphetamines, cocaine, or others) may cause hallucinations and psychosis and eventually schizophrenia. This is supported by a recent study showing that poly drug use is more associated with schizophrenia than cannabis use alone (Rognli et al., 2015). Furthermore, there are many risk factors associated with schizophrenia besides cannabis use, including urbanicity, comorbidity with other psychiatric disorders, and genetic factors. Future research should attempt to reveal which of these are the strongest

predictors of schizophrenia and whether these factors impact cannabis use.

Interactions between stress, cannabis use, and schizophrenia

Many studies show a link between cannabis use, stress, and schizophrenia. These links are greater in vulnerable populations (e.g. those exposed to childhood abuse) who have a family history of schizophrenia. Konings et al. (2012) found that childhood abuse moderated the effect of cannabis use on psychosis in a dose-dependent manner. The severity and frequency of abuse moderated the relationship between cannabis use and psychosis. Individuals who were subjected to sexual or physical abuse during childhood or early adolescence experienced an increase in the psychotic effects of cannabis. This demonstrated that cannabis use and childhood abuse can lead to symptoms of psychosis. Other studies have also found that childhood abuse can lead to the development of schizophrenia or trigger its onset in vulnerable populations. Konings et al. (2012) suggested that this interaction was probably not due to self-medication. Indeed, Cougnard et al. (2007) found that cannabis use, the stressors of childhood trauma, and coming from an urban area combined additively to produce increased psychotic symptoms in subjects both with and without baseline psychotic symptoms. The risk of psychotic experience was increased by the interaction between cannabis and adverse childhood experience, in a more than additive fashion (Harley et al., 2010). Along these lines, Houston et al. (2008) reported that teenagers who used cannabis under 16 years of age, combined with sexual abuse also under 16, had a 12 times greater risk for psychosis. It is important to note that a majority of these studies do not demonstrate a causal relationship. Nor have they identified whether the interaction between cannabis use and childhood resulted in the development of new psychotic symptom or the maintenance of current psychotic symptoms. As such, further exploration of the causal relationship between stress (e.g. childhood abuse), cannabis use, and schizophrenia is needed.

The concept of sensitization has been introduced to explain the additive effect of cannabis and stress on schizophrenia, whereby the repeated use of cannabis, particularly in adolescence when brain structures are being formed, may lead to an overreaction of the dopamine system (Cougnard et al., 2007). In an animal study, MacLean and Littleton (1977) reported that the administration of THC to rats experiencing stressful conditions changed dopamine metabolism in the corpus striatum. THC administration affects the endocannabinoid receptor CB1 which influences limbic system dopamine release (Cougnard et al., 2007). Levels of cortisol (the main hormone involved in the stress response) increase with stress and affect dopamine metabolism (Cougnard et al., 2007). The hypothalamic-pituitary-adrenal axis which is involved in the response to stress is partially regulated by the endocannabinoid system (Appiah-Kusi et al., 2015). It is plausible that cannabis use affects the stress response through its effect on the endocannabinoid system. On the other hand, Habets et al. (2011) argue that dopamine sensitization in schizophrenia, caused by repeated stress and cannabis use, may operate through the effects of reduced cortical thickening. The physiological condition underlying the interaction between stress and cannabis use is not known for sure. However, Mizrahi et al. (2014) propose that genetic vulnerability combines with stressors and/or drugs to produce psychosis.

Discussion

The link between cannabis use and schizophrenia is multifaceted and partially comprehended. It is well known that cannabis abuse is a risk factor for mental illness (McGee et al., 2000; Rey et al., 2002) especially psychosis (for a review, see Henquet et al., 2005; Radhakrishnan et al., 2014; Wilkinson et al., 2014).

The use of cannabis is not only related to psychotic patients (Ringen et al., 2008) but also increases the risk for schizophrenia (Moore et al., 2007; Manrique-Garcia et al., 2012). A wealth of evidence has demonstrated the role of the ECS in the pathophysiology of schizophrenia (Leweke et al., 2007; Morgan et al., 2013). Furthermore, there is evidence that alteration of the ECS plays a vital role in cannabis use (Realini et al., 2009) and schizophrenia (Muller-Vahl and Emrich, 2008; Koethe et al., 2009). Additionally, some of the neurocognitive impairments in cannabis users are similar to those observed in patients with schizophrenia (Solowij and Michie, 2007; Cohen et al., 2008; Gallinat et al., 2012). Paradoxically, there is growing evidence that cannabis use in patients with schizophrenia improves cognitive functions (Segev and Lev-Ran, 2012) and negative symptoms (DeRosse et al., 2010; Gorynia et al., 2014). Likewise, patients with schizophrenia who are cannabis users show less severe deficits in frontal gray matter compared to naïve first-episode patients with schizophrenia (Schnell et al., 2012). From

a clinical perspective, it is uncertain that the aforementioned findings associated with cannabis use in patients with schizophrenia are indeed specific to schizophrenia *per se* (Rentzsch et al., 2011; Wobrock et al., 2013).

It remains to be explored if any advantageous effects of ECS stimulation in the perspective of schizophrenia will prove to be of practical therapeutic value. Robson et al. (2014) investigated the therapeutic prospects of cannabinoids in schizophrenia. They concluded that cannabinoid medicine might have the potential to reduce the unwanted side effects of antipsychotic drugs and help control the associated metabolic problem, which is a part of the schizophrenia phenotype. Indeed, many of the potential side effects associated with cannabis use (e.g. psychosis) are attributed to the high levels of THC in recreational cannabis. Specifically, the acute administration of THC can cause schizophrenic like symptoms and cognitive impairments (Radhakrishnan et al., 2014; Iseger and Bossong, 2015) as well as increase the severity of symptoms in patients with schizophrenia. Conversely, there is mounting evidence that cannabinoids (CBD; the other main compound in cannabis) can counter these effects and have potential therapeutic applications for treating, or at least lowering, the risk of psychosis, cognitive impairments, anxiety, and euphoria (Bhattacharyya et al., 2010) as well as anti-inflammatory and neuroprotective properties. However, these effects are only prominent when the levels of CBD are higher than the THC levels in the cannabis. It is noteworthy that 5 and 10 year mortality risk in patients with schizophrenia was significantly lower in those who regularly smoked cannabis compared with non-cannabis patients (Koola et al., 2012). Such beneficial effects may be due to cognitive functions improvement, metabolic parameters improvement, and/or reduced stress. All these postulated hypotheses are equally plausible and accepted. However, these hypotheses are in need of replication and extension for their validity and to identify the effectiveness of CBD compared to antipsychotic drugs already in use.

Clinical implications and future directions

Schizophrenia is a common psychiatric disorder all over the world. Currently, there is no available laboratory test to diagnose schizophrenia, but instead, diagnosis depends mainly on the patients' symptomatology and the clinicians' observations. There are many possible combinations of symptoms for schizophrenia, and thus

there is a debate whether schizophrenia is a single disorder or a number of discrete syndromes (Tandon et al., 2008). Hence, behavioral and neurobiological marker studies will provide important information about the neuroplastic changes associated with cannabis abuse in patients with schizophrenia. Gaining a greater insight into the mechanisms of cannabis dependence in patients with schizophrenia will lead naturally to the development of pharmacotherapeutics and identifying objective laboratory tests for the diagnosis of schizophrenia. This knowledge may also aid cannabis cessation for individuals with schizophrenia as well as addicts without schizophrenia who express similar changes in cholinergic function.

It is clear that there is controversy in the current literature on cannabis effects on schizophrenia patients. While some studies have found cognitive deficits (e.g. Pope et al., 2001), others have found superior neurocognitive performance (e.g. Rabin et al., 2011) in schizophrenia patients who used cannabis. It may be that there is a clear lack of consistency when studies proceduralize and categorize the 'user' versus 'non-user' criterion to account for confounding variables such as frequency, amount, duration, and comorbid substances. Further, Bornstein et al. (1990) suggest that symptom severity and chronicity have to be considered in order to accurately examine potential moderators on effect size in cognitive functioning in schizophrenia patients. With this in mind, it is clear that the above mentioned findings are likely to be confounded by uncontrolled variables that can affect such factors. Variables such as duration of diagnosis, age of initial onset of symptoms, nature of cannabis use, and varying psychiatric symptoms need to be considered for studies.

Summary and conclusions

This review highlights the main findings in humans and animals concerning the effects of combining cannabis with schizophrenia. Where possible, one of the aims was to elucidate similarities and differences between investigations in humans and those carried out in animals. Our major question is does the co-existence of cannabis use and schizophrenia increase or lessen risks for compulsive use, toxicity, or both? The interaction between cannabis use and schizophrenia in rats would seem to bring that point into sharp focus. There is no doubt that cannabis is one of the most popular illicit drugs because of its intense euphoric effects and the accompanying myth

about its safety and ability to treat some human disorders. Therefore, to better gauge the extent of cannabis use and schizophrenia, we must rely on preclinical studies and human case reports. Such research should provide clear information and, in turn, inform prevention and intervention efforts.

References

Ameri, A. (1999). The effects of cannabinoids on the brain. Prog. Neurobiol. *58*, 315–348.

Appels, M.C., Sitskoorn, M.M., Vollema, M.G., and Kahn, R.S. (2004). Elevated levels of schizotypal features in parents of patients with a family history of schizophrenia spectrum disorders. Schizophr. Bull. *30*, 781–790.

Appiah-Kusi, E., Leyden, E., Parmar, S., Mondelli, V., McGuire, P., and Bhattacharyya, S. (2015). Abnormalities in neuroendocrine stress response in psychosis: the role of endocannabinoids. Psychol. Med. *46*, 1–19.

Arseneault, L., Cannon, M., Poulton, R., Murray, R., Caspi, A., and Moffitt, T.E. (2002). Cannabis use in adolescence and risk for adult psychosis: longitudinal prospective study. Br. Med. J. *325*, 1212–1213.

Awad, A.G. and Voruganti, L.L. (2015). Revisiting the 'self-medication' hypothesis in light of the new data linking low striatal dopamine to comorbid addictive behavior. Ther. Adv. Psychopharmacol. *5*, 172–178.

Bailey, E.L. and Swallow, B.L. (2004). The relationship between cannabis use and schizotypal symptoms. Eur. Psychiat. *19*, 113–114.

Barkus, E. and Lewis, S. (2008). Schizotypy and psychosis-like experiences from recreational cannabis in a non-clinical sample. Psychol. Med. *38*, 1267–1276.

Barkus, E., Morrison, P.D., Vuletic, D., Dickson, J.C., Ell, P.J., Pilowsky, L.S., Brenneisen, R., Holt, D.W., Powell, J., Kapur, S., et al. (2011). Does intravenous Delta9-tetrahydrocannabinol increase dopamine release? A SPET study. J. Psychopharmacol. *25*, 1462–1468.

Barnes, T.R., Mutsatsa, S.H., Hutton, S.B., Watt, H.C., and Joyce, E.M. (2006). Comorbid substance use and age at onset of schizophrenia. Br. J. Psychiat. *188*, 237–242.

Bhattacharyya, S., Morrison, P.D., Fusar-Poli, P., Martin-Santos, R., Borgwardt, S., Winton-Brown, T., Nosarti, C., O'Carroll, C.M., Seal, M., Allen, P., et al. (2010). Opposite effects of delta-9-tetrahydrocannabinol and cannabidiol on human brain function and psychopathology. Neuropsychopharmacology *35*, 764–774.

Bornstein, R.A., Nasrallah, H.A., Olson, S.C., Coffman, J.A., Torello, M., and Schwarzkopf, S.B. (1990). Neuropsychological deficit in schizophrenic subtypes: paranoid, nonparanoid, and schizoaffective subgroups. Psychiat. Res. *31*, 15–24.

Calvigioni, D., Hurd, Y.L., Harkany, T., and Keimpema, E. (2014). Neuronal substrates and functional consequences of prenatal cannabis exposure. Eur. Child. Adoles. Psy. *23*, 931–941.

Cannon, M. and Murray, R.M. (1998). Neonatal origins of schizophrenia. Arch. Dis. Child. *78*, 1–3.

Cardno, A.G. and Owen, M.J. (2014). Genetic relationships between schizophrenia, bipolar disorder, and schizoaffective disorder. Schizophr. Bull. *40*, 504–515.

Chambers, R.A. and Self, D.W. (2002). Motivational responses to natural and drug rewards in rats with neonatal ventral hippocampal lesions: an animal model of dual diagnosis schizophrenia. Neuropsychopharmacology *27*, 889–905.

Clausen, L., Hjorthoj, C.R., Thorup, A., Jeppesen, P., Petersen, L., Bertelsen, M., and Nordentoft, M. (2013). Change in cannabis use, clinical symptoms and social functioning among patients with first-episode psychosis: a 5-year follow-up study of patients in the OPUS trial. Psychol. Med. *44*, 117–126.

Cohen, M., Solowij, N., and Carr, V. (2008). Cannabis, cannabinoids and schizophrenia: integration of the evidence. Aust. N. Z. J. Psychiat. *42*, 357–368.

Cougnard, A., Marcelis, M., Myin-Germeys, I., De Graaf, R., Vollebergh, W., Krabbendam, L., Lieb, R., Wittchen, H.U., Henquet, C., Spauwen, J., et al. (2007). Does normal developmental expression of psychosis combine with environmental risk to cause persistence of psychosis? A psychosis proneness-persistence model. Psychol. Med. *37*, 513–527.

D'Souza, D.C., Abi-Saab, W.M., Madonick, S., Forselius-Bielen, K., Doersch, A., Braley, G., Gueorguieva, R., Cooper, T.B., and Krystal, J.H. (2005). Delta-9-tetrahydrocannabinol effects in schizophrenia: implications for cognition, psychosis, and addiction. Biol. Psychiat. *57*, 594–608.

Davis, G.P., Compton, M.T., Wang, S., Levin, F.R., and Blanco, C. (2013). Association between cannabis use, psychosis, and schizotypal personality disorder: findings from the National Epidemiologic Survey on Alcohol and Related Conditions. Schizophr. Res. *151*, 197–202.

De Petrocellis, L. and Di Marzo, V. (2010). Non-CB1, non-CB2 receptors for endocannabinoids, plant cannabinoids, and synthetic cannabimimetics: focus on G-protein-coupled receptors and transient receptor potential channels. J. Neuroimmun. Pharmacol. *5*, 103–121.

Dean, B., Sundram, S., Bradbury, R., Scarr, E., and Copolov, D. (2001). Studies on [³H]CP-55940 binding in the human central nervous system: regional specific changes in density of cannabinoid-1 receptors associated with schizophrenia and cannabis use. Neuroscience *103*, 9–15.

Deas, D. and Brown, E.S. (2006). Adolescent substance abuse and psychiatric comorbidities. J. Clin. Psychiat. *67*, e02.

Degenhardt, L., Hall, W., and Lynskey, M. (2003). Testing hypotheses about the relationship between cannabis use and psychosis. Drug Alcohol Depen. *71*, 37–48.

Degenhardt, L., Tennant, C., Gilmour, S., Schofield, D., Nash, L., Hall, W., and McKay, D. (2007). The temporal dynamics of relationships between cannabis, psychosis and depression among young adults with psychotic disorders: findings from a 10-month prospective study. Psychol. Med. *37*, 927–934.

DeRosse, P., Kaplan, A., Burdick, K.E., Lencz, T., and Malhotra, A.K. (2010). Cannabis use disorders in schizophrenia: effects on cognition and symptoms. Schizophr. Res. *120*, 95–100.

Dickey, C.C., McCarley, R.W., Niznikiewicz, M.A., Voglmaier, M.M., Seidman, L.J., Kim, S., and Shenton, M.E. (2005). Clinical, cognitive, and social characteristics of a sample of neuroleptic-naive persons with schizotypal personality disorder. Schizophr. Res. *78*, 297–308.

Ehrenreich, H., Rinn, T., Kunert, H.J., Moeller, M.R., Poser, W., Schilling, L., Gigerenzer, G., and Hoehe, M.R. (1999). Specific attentional dysfunction in adults following early start of cannabis use. Psychopharmacology (Berl.) 142, 295–301.

Emrich, H.M., Leweke, F.M., and Schneider, U. (1997). Towards a cannabinoid hypothesis of schizophrenia: cognitive impairments due to dysregulation of the endogenous cannabinoid system. Pharmacol. Biochem. Behav. 56, 803–807.

Esterberg, M.L., Goulding, S.M., McClure-Tone, E.B., and Compton, M.T. (2009). Schizotypy and nicotine, alcohol, and cannabis use in a non-psychiatric sample. Addict. Behav. 34, 374–379.

Fadda, P., Robinson, L., Fratta, W., Pertwee, R.G., and Riedel, G. (2004). Differential effects of THC- or CBD-rich cannabis extracts on working memory in rats. Neuropharmacology 47, 1170–1179.

Fanous, A.H., Neale, M.C., Gardner, C.O., Webb, B.T., Straub, R.E., O'Neill, F.A., Walsh, D., Riley, B.P., and Kendler, K.S. (2007). Significant correlation in linkage signals from genome-wide scans of schizophrenia and schizotypy. Mol. Psychiatr. 12, 958–965.

Foti, D.J., Kotov, R., Guey, L.T., and Bromet, E.J. (2010). Cannabis use and the course of schizophrenia: 10-year follow-up after first hospitalization. Am. J. Psychiat. 167, 987–993.

Fowler, I.L., Carr, V.J., Carter, N.T., and Lewin, T.J. (1998). Patterns of current and lifetime substance use in schizophrenia. Schizophr. Bull. 24, 443–455.

Gallinat, J., Rentzsch, J., and Roser, P. (2012). Neurophysiological effects of cannabinoids: implications for psychosis research. Curr. Pharm. Des. 18, 4938–4949.

Gallo, A., Bouchard, C., and Rompre, P.P. (2014). Animals with a schizophrenia-like phenotype are differentially sensitive to the motivational effects of cannabinoid agonists in conditioned place preference. Behav. Brain Res. 268, 202–212.

Gaoni, Y. and Mechoulam, R. (1971). The isolation and structure of delta-1-tetrahydrocannabinol and other neutral cannabinoids from hashish. J. Am. Chem. Soc. 93, 217–224.

Giuffrida, A., Leweke, F.M., Gerth, C.W., Schreiber, D., Koethe, D., Faulhaber, J., Klosterkötter, J., and Piomelli, D. (2004). Cerebrospinal anandamide levels are elevated in acute schizophrenia and are inversely correlated with psychotic symptoms. Neuropsychopharmacology 29, 2108–2114.

Glassman, A.H. (1993). Cigarette smoking: implications for psychiatric illness. Am. J. Psychiat. 150, 546–553.

Gorynia, I., Schwaiger, M., and Heinz, A. (2014). Effects of eye dominance (left vs. right) and cannabis use on intermanual coordination and negative symptoms in schizophrenia patients. Eur. Arch. Psy. Clin. N. 264, 683–695.

Goswami, S., Mattoo, S.K., Basu, D., and Singh, G. (2004). Substance-abusing schizophrenics: do they self-medicate? Am. J. Addict. 13, 139–150.

Green, A.I., Tohen, M.F., Hamer, R.M., Strakowski, S.M., Lieberman, J.A., Glick, I., Clark, W.S., and HGDH Research Group (2004). First episode schizophrenia-related psychosis and substance use disorders: acute response to olanzapine and haloperidol. Schizophr. Res. 66, 125–135.

Habets, P., Marcelis, M., Gronenschild, E., Drukker, M., and van Os, J. (2011). Reduced cortical thickness as an outcome of differential sensitivity to environmental risks in schizophrenia. Biol. Psychiat. 69, 487–494.

Harley, M., Kelleher, I., Clarke, M., Lynch, F., Arseneault, L., Connor, D., Fitzpatrick, C., and Cannon, M. (2010). Cannabis use and childhood trauma interact additively to increase the risk of psychotic symptoms in adolescence. Psychol. Med. 40, 1627–1634.

Harrison, P.J. and Eastwood, S.L. (2001). Neuropathological studies of synaptic connectivity in the hippocampal formation in schizophrenia. Hippocampus 11, 508–519.

Henquet, C., Krabbendam, L., Spauwen, J., Kaplan, C., Lieb, R., Wittchen, H.U., and Van Os, J. (2005). Prospective cohort study of cannabis use, predisposition for psychosis, and psychotic symptoms in young people. Br. Med. J. 330, 11.

Hickman, M., Vickerman, P., Macleod, J., Kirkbride, J., and Jones, P.B. (2007). Cannabis and schizophrenia: model projections of the impact of the rise in cannabis use on historical and future trends in schizophrenia in England and Wales. Addiction 102, 597–606.

Houston, J.E., Murphy, J., Adamson, G., Stringer, M., and Shevlin, M. (2008). Childhood sexual abuse, early cannabis use, and psychosis: testing an interaction model based on the National Comorbidity Survey. Schizophr. Bull. 34, 580–585.

Hutchings, D.E. and Dow-Edwards, D. (1991). Animal models of opiate, cocaine, and cannabis use. Clin. Perinatol. 18, 1–22.

Ilan, A.B., Gevins, A., Coleman, M., ElSohly, M.A., and de Wit, H. (2005). Neurophysiological and subjective profile of marijuana with varying concentrations of cannabinoids. Behav. Pharmacol. 16, 487–496.

Iseger, T.A. and Bossong, M.G. (2015). A systematic review of the antipsychotic properties of cannabidiol in humans. Schizophr. Res. 162, 153–161.

Jockers-Scherübl, M.C., Wolf, T., Radzei, N., Schlattmann, P., Rentzsch, J., de Castro, A.G.C., and Kühl, K.P. (2007). Cannabis induces different cognitive changes in schizophrenic patients and in healthy controls. Prog. Neuropsychopharmacol. Biol. Psychiat. 31, 1054–1063.

Khandaker, G.M., Barnett, J.H., White, I.R., and Jones, P.B. (2011). A quantitative meta-analysis of population-based studies of premorbid intelligence and schizophrenia. Schizophr. Res. 132, 220–227.

Koethe, D., Hoyer, C., and Leweke, F.M. (2009). The endocannabinoid system as a target for modelling psychosis. Psychopharmacology (Berl.) 206, 551–561.

Kohen, D. (2004). Diabetes mellitus and schizophrenia: historical perspective. Br. J. Psychiat. (Suppl.) 47, S64–S66.

Konings, M., Stefanis, N., Kuepper, R., De Graaf, R., Ten Have, M., Van Os, J., Bakoula, C., and Henquet, C. (2012). Replication in two independent population-based samples that childhood maltreatment and cannabis use synergistically impact on psychosis risk. Psychol. Med. 42, 149–159.

Koola, M.M., McMahon, R.P., Wehring, H.J., Liu, F., Mackowick, K.M., Warren, K.R., Feldman, S., Shim, J.C., Love, R.C., and Kelly, D.L. (2012). Alcohol and cannabis use and mortality in people with schizophrenia and related psychotic disorders. J. Psychiatr. Res. 46, 987–993.

Koskinen, J., Lohonen, J., Koponen, H., Isohanni, M., and Miettunen, J. (2009). Rate of cannabis use disorders in clinical samples of patients with schizophrenia: a meta-analysis. Schizophr. Bull. 36, 1115–1130.

Koskinen, J., Lohonen, J., Koponen, H., Isohanni, M., and Miettunen, J. (2010). Rate of cannabis use disorders in clinical samples of patients with schizophrenia: a meta-analysis. Schizophr. Bull. 36, 1115–1130.

Langer, O. and Halldin, C. (2002). PET and SPET tracers for mapping the cardiac nervous system. Eur. J. Nucl. Med. Mol. Imaging *29*, 416–434.

Large, M., Sharma, S., Compton, M.T., Slade, T., and Nielssen, O. (2011). Cannabis use and earlier onset of psychosis: a systematic meta-analysis. Arch. Gen. Psychiat. *68*, 555–561.

Leroy, S., Griffon, N., Bourdel, M.C., Olie, J.P., Poirier, M.F., and Krebs, M.O. (2001). Schizophrenia and the cannabinoid receptor type 1 (CB1): association study using a single-base polymorphism in coding exon 1. Am. J. Med. Genet. *105*, 749–752.

Leweke, F.M., Giuffrida, A., Wurster, U., Emrich, H.M., and Piomelli, D. (1999). Elevated endogenous cannabinoids in schizophrenia. Neuroreport *10*, 1665–1669.

Leweke, F.M., Giuffrida, A., Koethe, D., Schreiber, D., Nolden, B.M., Kranaster, L., Neatby, M.A., Schneider, M., Gerth, C.W., Hellmich, M., et al. (2007). Anandamide levels in cerebrospinal fluid of first-episode schizophrenic patients: impact of cannabis use. Schizophr. Res. *94*, 29–36.

Linszen, D.H., Dingemans, P.M., and Lenior, M.E. (1994). Cannabis abuse and the course of recent-onset schizophrenic disorders. Arch. Gen. Psychiat. *51*, 273–279.

MacLean, K.I. and Littleton, J.M. (1977). Environmental stress as a factor in the response of rat brain catecholamine metabolism to delta8-tetrahydrocannabinol. Eur. J. Pharmacol. *41*, 171–182.

Maki, P., Veijola, J., Jones, P.B., Murray, G.K., Koponen, H., Tienari, P., Miettunen, J., Tanskanen, P., Wahlberg, K.E., Koskinen, J., et al. (2005). Predictors of schizophrenia – a review. Br. Med. Bull. *73–74*, 1–15.

Malaspina, D., Owen, M.J., Heckers, S., Tandon, R., Bustillo, J., Schultz, S., Barch, D.M., Gaebel, W., Gur, R.E., Tsuang, M., et al. (2013). Schizoaffective disorder in the DSM-5. Schizophr. Res. *150*, 21–25.

Malone, D.T., Hill, M.N., and Rubino, T. (2010). Adolescent cannabis use and psychosis: epidemiology and neurodevelopmental models. Br. J. Pharmacol. *160*, 511–522.

Manrique-Garcia, E., Zammit, S., Dalman, C., Hemmingsson, T., Andreasson, S., and Allebeck, P. (2012). Cannabis, schizophrenia and other non-affective psychoses: 35 years of follow-up of a population-based cohort. Psychol. Med. *42*, 1321–1328.

Margolese, H.C., Malchy, L., Negrete, J.C., Tempier, R., and Gill, K. (2004). Drug and alcohol use among patients with schizophrenia and related psychoses: levels and consequences. Schizophr. Res. *67*, 157–166.

Mata, I., Rodriguez-Sanchez, J.M., Pelayo-Teran, J.M., Perez-Iglesias, R., Gonzalez-Blanch, C., Ramirez-Bonilla, M., Martinez-Garcia, O., Vazquez-Barquero, J.L., and Crespo-Facorro, B. (2008). Cannabis abuse is associated with decision-making impairment among first-episode patients with schizophrenia-spectrum psychosis. Psychol. Med. *38*, 1257–1266.

McCreadie, R.G. and Kelly, C. (2000). Patients with schizophrenia who smoke. Private disaster, public resource. Br. J. Psychiat. *176*, 109.

McEvoy, J.P., Meyer, J.M., Goff, D.C., Nasrallah, H.A., Davis, S.M., Sullivan, L., Meltzer, H.Y., Hsiao, J., Stroup, T.S., and Lieberman, J.A. (2005). Prevalence of the metabolic syndrome in patients with schizophrenia: baseline results from the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) schizophrenia trial and comparison with national estimates from NHANES III. Schizophr. Res. *80*, 19–32.

McGee, R., Williams, S., Poulton, R., and Moffitt, T. (2000). A longitudinal study of cannabis use and mental health from adolescence to early adulthood. Addiction *95*, 491–503.

Mizrahi, R., Kenk, M., Suridjan, I., Boileau, I., George, T.P., McKenzie, K., Wilson, A.A., Houle, S., and Rusjan, P. (2014). Stress-induced dopamine response in subjects at clinical high risk for schizophrenia with and without concurrent cannabis use. Neuropsychopharmacology *39*, 1479–1489.

Moghaddam, B. and Krystal, J.H. (2003). The neurochemistry of schizophrenia. Schizophrenia. S.R. Hirsch and D.R. Weinberger, eds. (Massachusetts: Blackwell Science), pp. 349–364.

Moore, T.H., Zammit, S., Lingford-Hughes, A., Barnes, T.R., Jones, P.B., Burke, M., and Lewis, G. (2007). Cannabis use and risk of psychotic or affective mental health outcomes: a systematic review. Lancet *370*, 319–328.

Morgan, C.J. and Curran, H.V. (2008). Effects of cannabidiol on schizophrenia-like symptoms in people who use cannabis. Br. J. Psychiat. *192*, 306–307.

Morgan, C.J., Page, E., Schaefer, C., Chatten, K., Manocha, A., Gulati, S., Curran, H.V., Brandner, B., and Leweke, F.M. (2013). Cerebrospinal fluid anandamide levels, cannabis use and psychotic-like symptoms. Br. J. Psychiat. *202*, 381–382.

Morrison, P.D. and Stone, J.M. (2011). Synthetic delta-9-tetrahydrocannabinol elicits schizophrenia-like negative symptoms which are distinct from sedation. Hum. Psychopharmacol. *26*, 77–80.

Mortensen, P.B. and Juel, K. (1993). Mortality and causes of death in first admitted schizophrenic patients. Br. J. Psychiat. *163*, 183–189.

Muller-Vahl, K.R. and Emrich, H.M. (2008). Cannabis and schizophrenia: towards a cannabinoid hypothesis of schizophrenia. Expert Rev. Neurother. *8*, 1037–1048.

Najolia, G.M., Buckner, J.D., and Cohen, A.S. (2012). Cannabis use and schizotypy: the role of social anxiety and other negative affective states. Psychiat. Res. *200*, 660–668.

Negrete, J.C., Knapp, W.P., Douglas, D.E., and Smith, W.B. (1986). Cannabis affects the severity of schizophrenic symptoms: results of a clinical survey. Psychol. Med. *16*, 515–520.

Pertwee, R.G. (2006). Cannabinoid pharmacology: the first 66 years. Br. J. Pharmacol. *147*, S163–S171.

Pope, H.G., Jr., Gruber, A.J., and Yurgelun-Todd, D. (2001). Residual neuropsychologic effects of cannabis. Curr. Psychiat. Rep. *3*, 507–512.

Potvin, S., Joyal, C.C., Pelletier, J., and Stip, E. (2008). Contradictory cognitive capacities among substance-abusing patients with schizophrenia: a meta-analysis. Schizophr. Res. *100*, 242–251.

Rabin, R.A., Zakzanis, K.K., and George, T.P. (2011). The effects of cannabis use on neurocognition in schizophrenia: a meta-analysis. Schizophr. Res. *128*, 111–116.

Radek, R.J., Miner, H.M., Bratcher, N.A., Decker, M.W., Gopalakrishnan, M., and Bitner, R.S. (2006). Alpha4beta2 nicotinic receptor stimulation contributes to the effects of nicotine in the DBA/2 mouse model of sensory gating. Psychopharmacology (Berl.) *187*, 47–55.

Radhakrishnan, R., Wilkinson, S.T., and D'Souza, D.C. (2014). Gone to pot – a review of the association between cannabis and psychosis. Front. Psychiatry *5*, 54.

Ramaekers, J.G., Moeller, M.R., van Ruitenbeek, P., Theunissen, E.L., Schneider, E., and Kauert, G. (2006). Cognition and motor control as a function of Δ9-THC concentration in serum and oral fluid: limits of impairment. Drug Alcohol Depen. *85*, 114–122.

Realini, N., Rubino, T., and Parolaro, D. (2009). Neurobiological alterations at adult age triggered by adolescent exposure to cannabinoids. Pharmacol. Res. *60*, 132–138.

Regier, D.A., Farmer, M.E., Rae, D.S., Locke, B.Z., Keith, S.J., Judd, L.L., and Goodwin, F.K. (1990). Comorbidity of mental disorders with alcohol and other drug abuse. Results from the Epidemiologic Catchment Area (ECA) study. J. Am. Med. Assoc. *264*, 2511–2518.

Rentzsch, J., Buntebart, E., Stadelmeier, A., Gallinat, J., and Jockers-Scherubl, M.C. (2011). Differential effects of chronic cannabis use on preattentional cognitive functioning in abstinent schizophrenic patients and healthy subjects. Schizophr. Res. *130*, 222–227.

Rey, J.M., Sawyer, M.G., Raphael, B., Patton, G.C., and Lynskey, M. (2002). Mental health of teenagers who use cannabis. Results of an Australian survey. Br. J. Psychiat. *180*, 216–221.

Rezvani, A.H., Tizabi, Y., Getachew, B., Hauser, S.R., Caldwell, D.P., Hunter, C., and Levin, E.D. (2008). Chronic nicotine and dizo-cilpine effects on nicotinic and NMDA glutamatergic receptor regulation: interactions with clozapine actions and attentional performance in rats. Prog. Neuropsychopharmacol. Biol. Psy-chiat. *32*, 1030–1040.

Ringen, P.A., Lagerberg, T.V., Birkenaes, A.B., Engn, J., Faerden, A., Jonsdottir, H., Nesvåg, R., Friis, S., Opjordsmoen, S., Larsen, F., et al. (2008). Differences in prevalence and patterns of substance use in schizophrenia and bipolar disorder. Psychol. Med. *38*, 1241–1249.

Robson, P.J., Guy, G.W., Di Marzo, V. (2014). Cannabinoids and schizophrenia: therapeutic prospects. Curr. Pharm. Des. *20*, 2194–2204.

Rodvelt, K.R., Kracke, G.R., Schachtman, T.R., and Miller, D.K. (2008a). Ketamine induces hyperactivity in rats and hypersen-sitivity to nicotine in rat striatal slices. Pharmacol. Biochem. Behav. *91*, 71–76.

Rodvelt, K.R., Schachtman, T.R., Kracke, G.R., and Miller, D.K. (2008b). NMDA receptor blockade augmented nicotine-evoked dopamine release from rat prefrontal cortex slices. Neurosci. Lett. *440*, 319–322.

Rognli, E.B., Berge, J., Hakansson, A., and Bramness, J.G. (2015). Long-term risk factors for substance-induced and primary psychosis after release from prison. A longitudinal study of substance users. Schizophr. Res. *168*, 185–190.

Rounsaville, B.J. (2007). DSM-V research agenda: substance abuse/psychosis comorbidity. Schizophr. Bull. *33*, 947–952.

Rubino, T. and Parolaro, D. (2015). The impact of exposure to can-nabinoids in adolescence: insights from animal models. Biol. Psychiat. *79*, 578–585.

Rubino, T., Realini, N., Guidali, C., Braida, D., Capurro, V., Castiglioni, C., Cherubino, F., Romualdi, P., Candeletti, S., Sala, M., et al. (2008). Chronic delta 9-tetrahydrocannabinol during adolescence provokes sex-dependent changes in the emotional profile in adult rats: behavioral and biochemical cor-relates. Neuropsychopharmacology *33*, 2760–2771.

Schiffman, J., Nakamura, B., Earleywine, M., and LaBrie, J. (2005). Symptoms of schizotypy precede cannabis use. Psychiat. Res. *134*, 37–42.

Schneider, M. and Koch, M. (2003). Chronic pubertal, but not adult chronic cannabinoid treatment impairs sensorimotor gat-ing, recognition memory, and the performance in a progres-sive ratio task in adult rats. Neuropsychopharmacology *28*, 1760–1769.

Schnell, T., Koethe, D., Daumann, J., and Gouzoulis-Mayfrank, E. (2009). The role of cannabis in cognitive functioning of patients with schizophrenia. Psychopharmacology (Berl.) *205*, 45–52.

Schnell, T., Kleiman, A., Gouzoulis-Mayfrank, E., Daumann, J., and Becker, B. (2012). Increased gray matter density in patients with schizophrenia and cannabis use: a voxel-based morpho-metric study using DARTEL. Schizophr. Res. *138*, 183–187.

Segev, A. and Lev-Ran, S. (2012). Neurocognitive functioning and cannabis use in schizophrenia. Curr. Pharm. Des. *18*, 4999–5007.

Semple, D.M., McIntosh, A.M., and Lawrie, S.M. (2005). Cannabis as a risk factor for psychosis: systematic review. J. Psychopharma-col. *19*, 187–194.

Sevy, S., Burdick, K.E., Visweswaraiah, H., Abdelmessih, S., Lukin, M., Yechiam, E., and Bechara, A. (2007). Iowa gambling task in schizophrenia: a review and new data in patients with schizo-phrenia and co-occurring cannabis use disorders. Schizophr. Res. *92*, 74–84.

Shrivastava, A., Johnston, M., Terpstra, K., and Bureau, Y. (2014). Cannabis and psychosis: neurobiology. Ind. J. Psychiat. *56*, 8–16.

Skosnik, P.D., Spatz-Glenn, L., and Park, S. (2001). Cannabis use is associated with schizotypy and attentional disinhibition. Schizophr. Res. *48*, 83–92.

Smart, R.G. and Ogborne, A.C. (2000). Drug use and drinking among students in 36 countries. Addict. Behav. *25*, 455–460.

Solowij, N. and Grenyer, B.F.S. (2002). Long-term effects of cannabis on psyche and cognition. Cannabis and Cannabinoids: Pharma-cology, Toxicology, and Therapeutic Potential. F. Grotenhermen and E. Russo, eds. (New York: Haworth Press), pp. 99–311.

Solowij, N. and Michie, P.T. (2007). Cannabis and cognitive dys-function: parallels with endophenotypes of schizophrenia? J. Psychiatr. Neurosci. *32*, 30–52.

Spano, M.S., Fattore, L., Cadeddu, F., Fratta, W., and Fadda, P. (2013). Chronic cannabinoid exposure reduces phencyclidine-induced schizophrenia-like positive symptoms in adult rats. Psychopharmacology (Berl.) *225*, 531–542.

Steeds, H., Carhart-Harris, R.L., and Stone, J.M. (2015). Drug models of schizophrenia. Ther. Adv. Psychopharmacol. *5*, 43–58.

Stella, N. and Piomelli, D. (2001). Receptor-dependent formation of endogenous cannabinoids in cortical neurons. Eur. J. Pharma-col. *425*, 189–196.

Stirling, J., Lewis, S., Hopkins, R., and White, C. (2005). Cannabis use prior to first onset psychosis predicts spared neurocogni-tion at 10-year follow-up. Schizophr. Res. *75*, 135–137.

Szutorisz, H., DiNieri, J.A., Sweet, E., Egervari, G., Michaelides, M., Carter, J.M., Ren, Y., Miller, M.L., Blitzer, R.D., and Hurd, Y.L. (2014). Parental THC exposure leads to compulsive heroin-seeking and altered striatal synaptic plasticity in the subse-quent generation. Neuropsychopharmacology *39*, 1315–1323.

Tandon, R., Keshavan, M.S., and Nasrallah, H.A. (2008). Schizophre-nia, "just the facts": what we know in 2008 part 1: overview. Schizophr. Res. *100*, 4–19.

Tantra, M., Kröcher, T., Papiol, S., Winkler, D., Röckle, I., Jatho, J., Burkhardt, H., Ronnenberg, A., Gerardy-Schahn, R., Ehrenre-ich, H., et al. (2014). St8sia2 deficiency plus juvenile cannabis exposure in mice synergistically affect higher cognition in adulthood. Behav. Brain Res. *275*, 166–175.

Trezza, V., Cuomo, V., and Vanderschuren, L.J. (2008). Cannabis and the developing brain: insights from behavior. Eur. J. Pharmacol. *585*, 441–452.

Tsiridis, E., Lusty, P.J., Narvani, A.A., and Tsapakis, E.M. (2003). Doctors' knowledge of exposure to ionising radiation: doctors' exposure to ionising radiation may be cause for concern. Br. Med. J. *327*, 1167.

Tunbridge, E.M., Bannerman, D.M., Sharp, T., and Harrison, P.J. (2004). Catechol-o-methyltransferase inhibition improves set-shifting performance and elevates stimulated dopamine release in the rat prefrontal cortex. J. Neurosci. *24*, 5331–5335.

Ujike, H. and Morita, Y. (2004). New perspectives in the studies on endocannabinoid and cannabis: cannabinoid receptors and schizophrenia. J. Pharmacol. Sci. *96*, 376–381.

van Nimwegen, L., de Haan, L., van Beveren, N., van den Brink, W., and Linszen, D. (2005). Adolescence, schizophrenia and drug abuse: a window of vulnerability. Acta Psychiatr. Scand. (Suppl.) *427*, 35–42.

Von Sydow, K., Lieb, R., Pfister, H., Hofler, M., Sonntag, H., and Wittchen, H.U. (2001). The natural course of cannabis use, abuse and dependence over four years: a longitudinal community study of adolescents and young adults. Drug Alcohol Depen. *64*, 347–361.

Weiser, M., Reichenberg, A., Grotto, I., Yasvitzky, R., Rabinowitz, J., Lubin, G., Nahon, D., Knobler, H.Y., and Davidson, M. (2004). Higher rates of cigarette smoking in male adolescents before the onset of schizophrenia: a historical-prospective cohort study. Am. J. Psychiat. *161*, 1219–1223.

Wilkinson, S.T., Radhakrishnan, R., and D'Souza, D.C. (2014). Impact of cannabis use on the development of psychotic disorders. Curr. Addict. Rep. *1*, 115–128.

Wobrock, T., Falkai, P., Schneider-Axmann, T., Hasan, A., Galderisi, S., Davidson, M., Kahn, R.S., Derks, E.M., Boter, H., Rybakowski, J.K., et al. (2013). Comorbid substance abuse in first-episode schizophrenia: effects on cognition and psychopathology in the EUFEST study. Schizophr. Res. *147*, 132–139.

Yucel, M., Bora, E., Lubman, D.I., Solowij, N., Brewer, W.J., Cotton, S.M., Pantelis, C. (2012). The impact of cannabis use on cognitive functioning in patients with schizophrenia: a meta-analysis of existing findings and new data in a first-episode sample. Schizophr. Bull. *38*, 316–330.

Zammit, S., Allebeck, P., Andreasson, S., Lundberg, I., and Lewis, G. (2002). Self reported cannabis use as a risk factor for schizophrenia in Swedish conscripts of 1969: historical cohort study. Br. Med. J. *325*, 1199.

Zammit, S., Moore, T.H., Lingford-Hughes, A., Barnes, T.R., Jones, P.B., Burke, M., and Lewis, G. (2008). Effects of cannabis use on outcomes of psychotic disorders: systematic review. Br. J. Psychiat. *193*, 357–363.

Zuardi, A.W., Shirakawa, I., Finkelfarb, E., and Karniol, I.G. (1982). Action of cannabidiol on the anxiety and other effects produced by Δ9-THC in normal subjects. Psychopharmacology (Berl.) *76*, 245–250.